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CENTRAL INTELLIGENCE AGENCY

REPORT NO [redacted]

INFORMATION REPORT

CD NO 25X1A

COUNTRY East Germany

DATE DISTR 30 October 1953

SUBJECT Extent of Pharmaceutical Research Effort at Gehe & Company, Dresden

NO. OF PAGES 4

PLACE ACQUIRED [redacted]

NO. OF ENCLS (LISTED BELOW) 25X1A

DATE OF INFO.

SUPPLEMENT TO REPORT NO

[redacted] 25X1X

1. The research laboratories of Gehe & Company, Dresden, were located in the Institut fuer Farben und Textilchemie of the Technische Hochschule, Dresden, from April 1949 until August 1952. These facilities were used by Gehe to investigate and establish methods for the preparation of pharmaceuticals which were subsequently produced on a commercial scale by Gehe & Company and by the Arzneimittelwerk-Dresden (A.D). The A.D incorporated Gehe into its organization in 1952.

2. The director of the Institut fuer Farben und Textilchemie was Prof. Dr.-Ing. Walter Koenig, a member of the faculty of the Technische Hochschule, as well as chief of the chemistry section of Gehe's research organization. Dr. Koenig's assistant was Dr. Walter Siebeck. These men were given a free hand in the pursuit of their work and no apparent direction was supplied from government sources. However, because of the great shortage of chemical supplies in the DDR, their work was confined to investigating those pharmaceuticals for which there was the greatest need and for which sufficient raw materials were available. The following products were given particular attention:

a. Methylthiouracil

This was one of the more important products for which a production process was developed. Considerable success was obtained in the DDR in the application of methylthiouracil for therapy of goiter. The high incidence of this disease, particularly in young people, was attributed to the abnormal consumption of cabbage, kohlrabi, radishes, and similar plants as the sole vegetable source. The synthesis of methylthiouracil consisted of the condensation of aceto-acetic ester with urea, in which water and alcohol were split out to yield the heterocyclic ring compound (methylthiouracil).

b. Corvitol (beta-pyridine carboxylic acid diethylamide)

In the DDR, Corvitol was prepared from raw nicotine because of the non-availability of nicotinic acid as a raw material. The synthesis was carried out according to a method described in "Organic Syntheses" (further reference data not recalled by source), whereby nitric acid was used as an oxidizing agent and the methylpyrrolidine split off by using iron as a

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catalyst. This reaction had to be maintained at a temperature of 50-60°C. in order to prevent too rapid oxidation.

The diethylamide of nicotinic acid was obtained by treating the acid chloride with diethylamine. Originally thionylchloride was used in this step, but when the latter product was no longer available on the DAF it was discovered that phosphorus trichloride was also suitable for the formation of the acid chloride. The phosphoric acid formed in the reaction did not destroy the acid chloride. The reaction could be carried out in benzene solution. This procedure had not been known to the [illegible] at Goho & Company, nor had it been described in the literature available in Dresden.

The nicotinic acid chloride was converted to the hydrochloride of nicotinic acid diethylamide by treatment with diethylamine. The diethylamide salt was decomposed with sodium hydroxide and the free base purified by distillation under high vacuum. The fraction with the appropriate boiling point was separated from the distillate and retained.

c. Tetraethylammonium bromide

This product was prepared for therapy of peripheral circulatory disturbances, such as those found in Raynaud's disease or in gangrenous conditions. No special difficulties were encountered in the production of this compound, provided pure raw materials were used. The [illegible] was prepared by combining pure triethylamine and ethyl bromide under cooling. The compound so obtained began to crystallize out after a short period of standing. The crystals of tetraethylammonium bromide were purified to hold free triethylamine so that the final product was hygroscopic. Many patients, particularly elderly cases, showed an idiosyncrasy to tetraethylammonium bromide and went into a state of shock. The product was sold on the market in a 1 to 2 percent solution, but it was recommended that a 0.5 cc. test dose always be administered before use.

d. Indigocarmine

This dyestuff, the sodium salt of indigo disulfonic acid, was prepared for intravenous injections and employed as an indicator of kidney function. The dye is normally excreted by the kidneys and the [illegible] of each kidney can be observed cystoscopically in the bladder.

Indigo vat dye was treated with equivalent quantities of concentrated sulfuric acid, under external cooling, to produce the disodium salt of indigo. Addition of solid sodium carbonate precipitated the sodium salt. This was easily soluble in water and had to be isolated out of salt formed with sodium chloride. The final product was prepared as a 0.5 percent solution of the salt in physiological saline and sealed in ampules. It was discovered that the product contained traces of sodium chloride and it was, therefore, necessary to control the concentration of the solution to be sealed in ampules. The [illegible] for the quantitative control of concentration utilized the Zeiss-Pulfrich-Stufenphotometer. The company also received complaints that certain batches of the dyestuff precipitated out of solution. The cause of this could never be clearly established. In an attempt to avoid this, a less concentrated solution was used. After repeated testing in various urological clinics it was shown that solutions with a concentration as low as 0.2 per cent still produced a sufficient color contrast to be observed with the cystoscope in the bladder.

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e. Polymethine dyestuffs

A large part of the activity in the research laboratory in the Technische Hochschule consisted of the preparation of dyestuffs of the polymethine type. The discovery of this dyestuff class and the clarification of the course of the chemical reactions occurring during the synthesis of the compounds was the accomplishment of Prof. Dr. Konig. Pieblock, under the direction of Dr. Konig, submitted his doctorate thesis on the preparation of new polymethine dyes from [illegible] highly active substances. (See Attachment [illegible]). By virtue of their theoretically possible activity (through double molecule formation or incorporation of active, auxochrom groups), these new substances were expected to yield a greater biological activity than the original compounds. The polymethine dyes, whose synthesis was achieved from relatively simple substances, were thought to be worthwhile agents for pharmaceutical purposes. Unfortunately, it was not possible to carry out bacteriological or pharmaceutical investigations of these new products after they were synthesized.

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f. Tetraiodophenolphthalein

g. [redacted]

[redacted]

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A Summary of Thesis on Poly[illegible] Dyes by Drs. [illegible]

"Contributions to Chemotherapy through Synthesis of Streptopol[illegible] Dyes from Physiologically Active, and [illegible] Primary Amines."

Doctorate thesis presented at the Technische [illegible], October 11, 1951, by Dr. Walter Siebach, under the direction of [illegible] Walter Koenig and Prof. Dr.-Ing. [illegible].

The purpose of the project was to synthesize [illegible] products from [illegible] active substances in order to incorporate [illegible] varied effectiveness.

A series of new "streptopoly[illegible]" dyes [illegible] were synthesized from known [illegible] of compounds prepared were as follows:

Type I: dyes containing [illegible] novocain.

Type II: dyes with a [illegible] condensations of [illegible].

Type III: dyes with a [illegible] 1,5-PAS, novocain, and [illegible].

Type IV: dyes with [illegible] p-aminobenzoic acid and [illegible].

Type V: dyes with carbamine [illegible] prepared from aniline [illegible] and nicotinic acid di[illegible].

Type VI: compounds with an N-[illegible] materials as Type V.

The thesis presented nothing more than the [illegible] or pharmacological testing of the products [illegible] the author, the chemical composition of the new products [illegible] of new or increased physiological activity.